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BY: Helene Gabel DATE: January 3, 2003

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	Patent Application of Eugene Roussel	: Group Art Unit: **1642**
Appln. No.:	09/756,978	: Examiner: Misook Yu, Ph.D.
Filed:	January 9, 2001	: Conf. No. 6809
For:	THERAPEUTIC MODULATION OF THE TUMOR INFLAMMATORY RESPONSE	: Attorney Docket No. **10582-1US**

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1-13-03

DECLARATION OF DR. EUGENE ROUSSEL PURSUANT TO 37 C.F.R. §1.132

The following is an overview of this Declaration:

- Items 1-6 relate to **personal information** identifying me and some of my qualifications
- Items 7-10 relate to the **field of the invention** and the **level of skill** in the art
- Items 11-25 relate to **background and prior art** information to acquaint the Examiner with what was known at the time my patent application was filed
- Items 26-50 include my comments regarding the Examiner's enablement rejection
  - Items 28-38 relate to how a skilled worker in the field of the invention would understand **what is disclosed** in my patent application
  - Items 39-47 relate to the **need for relatively little experimentation** required to practice my invention
  - Items 47-49 include my comments regarding the lack of **working examples** in my patent application.

I hereby declare as follows:

Personal

1. I am the same Eugene Roussel who is named as the inventor of the invention described and claimed in the patent application referenced above ("my patent application").

2. Since February 2000, I have been the Chief Executive Officer and Scientific Director of BioTHER Corporation, based in Houston, Texas.

3. I have earned the following academic degrees: a) in 1990, a Ph.D. in immunology from the University of Manitoba in Winnipeg, Canada; b) in 1984, an M.S. in medical microbiology, from Laval University, Ste-Foy, in Quebec, Canada; c) in 1981, a B.S. in microbiology, from Laval University, Ste-Foy, in Quebec, Canada; and d) in 1978, a D.E.C. (undergraduate college degree in sciences, literature, and philosophy) from St. Augustin College in Quebec, Canada.

4. I have been involved in research relating to human inflammation and the tumor inflammatory response since at least 1985, including research performed at the University of Manitoba (Winnipeg, Canada), the M.D. Anderson Cancer Center (Houston, Texas), and the Baylor College of Medicine (Houston, Texas).

5. I am the author of 2 books and more than 30 published articles and abstracts relating to human inflammation and the tumor inflammatory response. I have been invited to speak to colleagues regarding these topics at no fewer than 10 seminars.

6. I am the recipient of no fewer than 8 scientific awards, including (in 1992) the Upjohn Award for Scientific Merit at the 83rd Annual Meeting of the American Association for Cancer Research and (in 1987) the International Presidential Award for making the best presentation at the 11th International Reticuloendothelial Society Congress.

Field of Technology

7. The invention for which I have filed my patent application relates to the field of cancer therapy.

8. The level of skill in this field is very high. Skilled workers who would practice my invention would typically be clinical oncologists.

9. In addition to their medical degree, clinical oncologists often have earned one or more other advanced degrees, will have performed a medical internship under the guidance of one or more other experienced clinical oncologists, and will likely have several years of additional experience. Clinical oncologists are accustomed to carefully observing cancer patients and the effects that therapy administered to those patients has upon the patients

and their tumors. Such oncologists are also accustomed to modifying the anti-cancer therapeutic regimes of patients having tumors to account for individual differences in patient responses to the regimes.

10. The responses of individual patients to pharmacological agents and combinations of such agents is known to vary to some degree. However, the activity attributable to each of the agents recited in the claims, within the dose ranges described in my patent application, was relatively well known at the time the application was filed. A skilled worker in this field is able to adjust the dosage of such agents to achieve the effects described in my application for substantially any individual patient.

Introduction to the Invention and the State of the Prior Art

11. My invention includes a therapeutic method that alleviates a tumor in a human patient by inducing the patient's immune system to attack and kill tumor cells.

12. Killing of tumor cells by a patient's immune system is a normal function of the immune system, as indicated in the enclosed chapter by Greenberg (1997; In: Medical Immunology, 9th ed., Stites et al., Eds., Appleton & Lange, Stamford, Connecticut, pp. 631-639; see the highlighted portion of page 634 and the first highlighted portion of the paragraph bridging pages 635 and 636). The enclosed abstract by Sheu et al. (1999, J. Formos. Med. Assoc. 98:730-735) also indicates that existence of a host immune response against tumor cells was known.

13. The host anti-tumor immune response sometimes fails to recognize tumor cells, leading to development of a tumor, as recognized in the portions of Greenberg and Sheu referred to in the preceding paragraph. Greenberg (see the second highlighted portion of the paragraph bridging pages 635 and 636) also indicates that it was credible that one could develop a therapeutic method to induce an effective anti-tumor immune response, even if such methods were not then known.

14. Helper T lymphocytes ("Th cells") were understood to be principal orchestrators of the human immune response at the time my patent application was filed. As

indicated in the enclosed chapter by Parslow (1997; In: Medical Immunology, 9th ed., Stites et al., Eds., Appleton & Lange, Stamford, Connecticut, pp. 63-73), it was recognized that Th cells activate both cytotoxic T cells ("Tc cells") and antibody-secreting plasma cells.

15. At the time my patent application was filed, it was understood that at least two distinct Th cell subsets existed, designated Th1 and Th2 (see, e.g., Romagnani, Ann. Allergy Asthma Immunol. 85:9-18, of record). As indicated, for example by Romagnani and in the paragraph bridging pages 1 and 2 of the patent application, Th1 cells and Th2 cells produce different characteristic sets of cytokines.

16. Immune responses that are dominated by activation of Th1 cells are characterized by proliferation of Tc cells. As a result, a significant cytotoxic effect is exerted at the site of the immune response (see Romagnani and my patent application at page 2, lines 4-12) against the immunogen for which the Tc cells are specific. This type of an immune response is designated a "type 1" inflammatory response. Type 1 inflammatory responses are characterized by the presence of certain cytokines at the site of inflammation, including interferon-gamma (IFN-g), tumor necrosis factor-beta (TNF-b), and interleukin-2 (IL-2).

17. Immune responses that are dominated by activation of Th2 cells are characterized by induction of humoral immunity (e.g., proliferation of antibody-producing B cells). This type of an immune response is designated a "type 2" inflammatory response. A type 2 inflammatory response generally induces significantly less cytotoxicity of antigen-bearing cells at the site of the inflammatory response than does a type 1 inflammatory response. Type 2 inflammatory responses are characterized by the presence of certain cytokines at the site of inflammation, including interleukin-4 (IL-4) and granulocyte-macrophage colony-stimulating factor (GMC-SF).

18. Typically, a significant portion of the mass of a tumor is made up of lymphocytes, designated tumor-infiltrating lymphocytes ("TILs"). The Th cells that are found among the TILs in non-regressing tumors are predominantly Th2 cells (Roussel et al., 1996, Clin. Exp. Immunol. 105:344-352; Whiteside et al., 1992, Cancer Immunol. Immunother. 39:15-21, both of record), including lymphocytes that are reactive with the patient's tumor (Greenberg, *supra* at 636). Predominance of Th2 cells in the tumor induces a type 2

inflammatory response in the tumor. The type 2 inflammatory response does not result in significant killing of tumor cells, and may even inhibit tumor cell cytotoxicity mediated by any Th1 cells that are present in the tumor.

19. Many researchers have suggested that induction of tumor cell death could be effected by modulating the type 2 inflammatory response in a non-regressing tumor in some way that the inflammatory response instead has the characteristics of a type 1 response. However, none of these previous researchers disclosed or suggested that the methods claimed in my patent application could be used to achieve induction of tumor cell death in a patient. A partial list of references that discuss the desirability of modulating a type 2 tumor inflammatory response to achieve a type 1 inflammatory response is as follows.

- Gorelik et al., 1994, Cancer Immunol. Immunother. 39:117-126, of record
- Pellegrini et al., 1996, Cancer Immunol. Immunother. 42:1-8, of record
- Goedegebuure et al., 1997. Cell Immunol. 175:150-156, of record
- Fujimoto et al., 1997, J. Immunol. 158:5619-5626, of record
- Okamoto et al., 1997, Int. J. Cancer 70:598-605, of record
- Stein et al., 1998, Eur. J. Med. Res. 3:194-202, of record
- Li et al., 1998, J. Surg. Oncol. 67:221-227, of record.

Based on the disclosures of these references, and from the knowledge in the art that Th cells can be induced to exhibit either a type 1 or a type 2 inflammatory response phenotype, skilled workers in this field would understand that a type 2 inflammatory response can be converted to a type 1 inflammatory response.

20. At least five groups of researchers have demonstrated that lymphocytes that exhibit a type 1 inflammatory response phenotype can induce tumor cell death and cause tumor regression *in vivo* (Xiang et al., 2000, J. Interferon Cytokine Res. 20:349-354; To et al., 2000, Laryngoscope 110:1648-1654; Wong et al., 2000, Br. J. Dermatol. 143:91-98; Lowes et al., 1997, J. Invest. Dermatol. 108:914-919; Khar et al., 1997, Clin. Exp. Immunol. 110:127-131, all of record). The results reported by these five groups are described in the following three items.

21. Xiang implanted VKCK tumor cells into mice. VKCK tumor cells are ordinarily poorly immunogenic and grow aggressively when implanted into mice. Xiang engineered two subsets of VKCK tumor cells such that cells of each of the two engineered groups would constitutively secrete a cytokine and induce nearby leukocytes to exhibit a type 1 inflammatory response when the engineered cells were implanted. Xiang observed that non-engineered VKCK tumor cells grew aggressively in mice and that the engineered VKCK tumor cells disappeared (and were presumably killed). Xiang also observed the cytokines secreted in tumors of mice into which the various types of tumor cells were implanted. They observed that IL-4 (i.e., a cytokine characteristic of a type 2 inflammatory response) was secreted by T cells obtained from tumors derived from non-engineered cells, and that little IFN-g was secreted by these T cells. They therefore concluded that a type 2 inflammatory response occurred in the aggressively growing tumors. Xiang also observed that relatively high levels of IFN-g, but relatively low levels of IL-4, were secreted by T cells obtained from tumors derived from the engineered VKCK tumor cells. Xiang concluded that these T cells exhibited a type 1 inflammatory response, and that the observed tumor cell death and tumor regression was attributable to the type 1 T cells that occurred in tumors of mice implanted with engineered cells.

The skilled worker in this field would consider the Xiang reference to be probative of the principle that substituting a type 1 inflammatory response in place of a type 2 inflammatory response in a tumor *in vivo* leads to induction of tumor cell death.

22. To et al. injected mice with MCA 205 tumor cells, which grew into tumors in non-treated mice. Lymphocytes obtained from the mice were expanded *ex vivo* in one of two environments. In one environment, the lymphocytes were expanded in the presence of cytokines that are characteristic of a type 1 inflammatory response, so that Th cells were induced to become Th1 cells. In the other environment, the lymphocytes were expanded in the presence of cytokines that are characteristic of a type 2 inflammatory response, so that Th cells were induced to become Th2 cells. The two groups of lymphocytes were separately injected intravenously into tumor cell-bearing mice. The anti-tumor-cell efficacy of the two groups of lymphocytes was compared. The lymphocytes having a type 1 inflammatory response

phenotype exhibited significantly greater tumor cell-killing efficiency than lymphocytes having a type 2 inflammatory response phenotype.

The skilled worker in this field would consider the To et al. reference to be probative of the principle that inducing a type 1 inflammatory response in a tumor *in vivo* leads to induction of tumor cell death.

23. Further evidence that supports the mechanism of action underlying the methods I claim in my patent application is found in the reference by Wong et al. Wong studied human basal cell carcinomas (BCCs), which progressively grow *in vivo*. Some BCCs regress spontaneously for reasons that are not fully understood. Wong compared cytokine profiles in regressing and progressing BCCs. Wong found that regressing BCCs exhibit cytokine profiles that are characteristic of a type 1 inflammatory response, and that progressing BCCs exhibit cytokine profiles that are characteristic of a type 2 inflammatory response. Similar results were reported in the reference by Lowes et al., for spontaneously regressing human primary melanomas and in the reference by Khar et al., for spontaneously regressing AK-5 histiocytomas.

The skilled worker in this field would consider the Wong et al., Lowes et al., and Khar et al. references to be probative of an association between occurrence of a type 1 inflammatory response in a human tumor and regression of the tumor (i.e., induction of death of tumor cells).

24. Numerous references (hereafter, "the BCG references") describe an important recent improvement in alleviation of superficial bladder cancer. These references include Lamm, 1992, Urol. Clin. North Am. 19(3):573-580; Prescott et al., 2000, Clin. Infect. Dis. 31(Suppl. 3):S91-S93; Saint et al., 2000, Prog. Urol. 10(6):1118-1126; Bohle, 2000, Eur. Urol. 37(Suppl. 1):1-8; and Patard et al., 1998, Urol. Res. 26(3):155-159. An abstract of each of these references is enclosed with this Declaration.

Intravesicular injection of a suspension of Bacillus Calmette-Guerin (BCG) in patients afflicted with superficial bladder tumors eradicates the tumors in a significant fraction of patients and decreases tumor burden in others. Several groups have investigated and reported the mechanism of action of action of anti-tumor BCG treatment. As indicated in the

Prescott reference, responsiveness to BCG treatment involves a local immune response induced at the site of BCG administration, and that this response involves activation of Th cells in the patient. The Saint reference discloses that the immune response induced upon BCG treatment is a type 1 inflammatory response (i.e., characterized by intratumoral release of inflammatory cytokines such as IFN-g and IL-2 and by activation of immune cell-mediated cytotoxicity directed against tumor cells). The Patard reference confirms that the cytokines that are found in the urine of patients treated intravesicularly with BCG are those (IL-2 and IFN-g) that are characteristic of type 1 inflammatory responses. The Bohle reference discloses that the type 1 inflammatory response induced upon BCG treatment is correlated with the anti-tumor response observed in patients. The Chin reference demonstrates that another (i.e., non-BCG) mycobacterial cell wall component is able to invoke a type 1 inflammatory response in superficial bladder tumors, and that this type 1 inflammatory response also induces tumor cell death.

Taken together, the BCG references demonstrate to skilled workers in this field that a type 1 inflammatory response can be induced *in vivo* in superficial bladder tumors by intravesicularly administering an inflammation-inducing mycobacterial product, and that the induced inflammatory response is correlated with induction of tumor cell death. In view of the BCG references, the skilled worker would understand that a method of inducing a type 1 inflammatory response in a human tumor would lead to induction of tumor cell death *in vivo*.

25. Based on what was known in the art at the time my patent application was filed (including the Xiang, To, Wong, Lowes, and Khar references), a skilled worker in this field would understand that occurrence of a type 1 inflammatory response in a tumor (whether brought about by spontaneous occurrence of a type 1 response or by induced conversion of a type 2 to a type 1 response) would lead to death of cells of the tumor. Based on the BCG references, a skilled worker in this field would understand that it is possible to induce an anti-tumor type 1 inflammatory response in a human patient *in vivo*.

The Office Actions

26. I have read the Office Action issued by the Examiner and dated 10 December 2002 (Paper No. 8) and the Office Action issued by the Examiner and dated 3 July 2002 (Paper No. 11). I also participated in a telephone interview conducted on 4 September 2002 among Examiner Natalie Davis, Examiner Tony Caputa, and my legal representative and a second telephone interview conducted on 2 January 2003 among Examiner Misook Yu, Examiner Tony Caputa, and my legal representative. I believe that part of the reason why Examiner Davis made and sustained certain rejections is because the Examiner, with all the respect due to her, is not a clinical oncologist and does not appreciate how a skilled worker in this field would use the information contained in my patent application.

27. Examiner Davis' comments in the Office Actions and the telephone interview indicate that she believes that it is unpredictable whether the agents recited in the claims in my patent application can be used to alleviate a tumor in humans. However, the Examiner does not adequately appreciate that the *in vivo* activity of each of the agents was known before I made my invention.

The methods that I have invented and claimed in my patent application combine the known activities of these known agents in a way that was not previously considered by others. In view of the disclosure provided in my patent application, skilled workers in this field will understand how the known activities of these known agents can be synergistically used to induce a localized anti-tumor type 1 inflammatory response in a human patient and to thereby induce death of tumor cells in the patient.

In the following items 28 to 38, I explain why a skilled worker in this field would understand my claimed methods to induce tumor cell death in human patients, in view of what is disclosed in my patent application and the prior art.

How a Skilled Worker in This Field Would Understand my Patent Application

28. The logic underlying operation of the methods claimed in my patent application was set forth in the Amendment and Request for Reconsideration filed by my legal representative on 10 April 2002. They are reproduced here in a modified form.

Very briefly, death of tumor cells in a human patient is induced by initiating, promoting, or both initiating and promoting a type 1 inflammatory response directed against the tumor cells in the patient. The type 1 response is induced by locally administering an antigen-releasing agent (see item 29), a leukocyte attractant (see item 30), IFN-g (see item 31), and a second type 1 inflammatory response-promoting agent (IR1-promoting agent, see item 31) to the tumor, as recited in claim 1 of my patent application. Administration of additional agents (see items 34 to 37 and claims 37-66 in my patent application) can enhance the efficacy or duration of the anti-tumor response.

29. Antigen-Releasing Agent. As discussed in my patent application at page 10, lines 9-17, local administration of an antigen-releasing agent to a tumor induces *in vivo* release of antigens from tumor cells and induces immune responses which are specific for tumor cells. This response is known in the art, as evidenced, for example, by the Gallucci et al. reference (2001, Curr. Op. Immunol. 13:114-119; of record), which summarizes the knowledge in the field at about the time the application was filed, with regard to release of factors by damaged tissues. Release of antigens from tumor cells provides a substrate which can be acted upon by leukocytes attracted to the tumor site in order to render the resulting inflammatory response specific for tumor cells. Release of antigens from tumor cells also establishes a gradient of antigen which can chemically 'direct' activated immune cells to the tumor site.

30. Leukocyte Attractant. As discussed in my patent application at page 10, lines 18-21, and at page 15, lines 22-29, local administration of one or more leukocyte attractants induces recruitment of leukocytes to the tumor site. It is well known that leukocytes are involved in mobilization of an immune response. Attraction of leukocytes to the site at which the chemokine is administered *in vivo* is disclosed, for example, in the Mantovani reference (1999, Immunol. Today 20:254-257; of record). The relevance of leukocytes attracted to the site becomes apparent below.

31. IFN-g and a Second Type 1 Inflammatory Response-Promoting Agent. As discussed in my patent application at page 10, line 22, through page 11, line 9, and at page 18, lines 5-12, local administration of type 1 inflammatory response-promoting agents induces leukocytes at the tumor site to exhibit a type 1 inflammatory response. Part of the type 1

inflammatory response is a cytotoxic response. Thus, leukocytes that are attracted to the tumor site interact with antigens released from tumor tissue and are induced (i.e., by the type 1 inflammatory response-promoting agents) to mount a cytotoxic response against tumor cells, thereby killing some or all of the tumor cells and alleviating the tumor. It was known at the time I filed my patent application that the presence of interferon-gamma and other cytokines at a tumor site was correlated with induction of a tumor-specific host anti-tumor immune response *in vivo* (see, Sadanaga et al., 1999, J. Immunother. 22:315-323, abstract of record).

The physiological activities of the agents disclosed in my patent application as type 1 inflammatory response-promoting agents (i.e., IL-2, IL-12, tumor necrosis factors-alpha {TNF-a} and -beta {TNF-b}, and IFN-g) were known at the time my patent application was filed, as disclosed for example in Oppenheim et al., 1997, In: Medical Immunology, 9th ed., Stites et al., Eds., Appleton & Lange, Stamford, Connecticut, pp.146-160 (see the highlighted portions of the enclosed copy). These activities are discussed in the following paragraph.

Interferon-gamma activates cells that mediate cytotoxic immune cells, including Tc cells, and inhibits proliferation of Th2 cells (i.e., enhancing type 1 inflammation and inhibiting type 2 inflammation; see Oppenheim, p. 158). Interleukin-2 promotes proliferation of activated T cells and enhances their cytotoxicity (see paragraph bridging pages 154 and 155 of Oppenheim). Interleukin-12 also promotes proliferation of activated T cells, and selectively induces Th cells to differentiate into Th1 cells (rather than into Th2 cells; see Oppenheim, p. 160). Tumor necrosis factor-alpha and -beta enhance activation and proliferation of Th cells (see Oppenheim, p. 147).

The methods claimed in my patent application involve using both IFN-g and a second IR1-promoting agent (e.g., one of IL-2, IL-12, TNF-a, and TNF-b) to induce type 1 inflammation locally in the patient's tumor. A skilled worker in this field would understand that contacting Th leukocytes with IFN-g *in vivo* will inhibit both proliferation of Th2 cells and differentiation of Th0 cells into Th2 cells, thereby limiting or preventing an increase in the number of Th2 cells in the tumor. Use of a second IR1-promoting agent enhances proliferation of Th1 cells that are present in the tumor and differentiation of Th0 cells into Th1 cells, thereby increasing the number of Th1 cells in the tumor. In this way, any type 2 inflammatory response

that occurs in the tumors is, over time, converted to a type 1 inflammatory response, and any type 1 inflammatory response in the tumor is enhanced.

In view of the disclosure in my patent application, a skilled worker in this field would understand that local administration of IFN-g and a second IR1-promoting agent, together with local administration to the tumor of an antigen-releasing agent and a leukocyte attractant will lead to induction of an anti-tumor type 1 inflammatory response in the tumor.

32. Items 29 to 31 address the agents common to all of the claims in my patent application. In view of the physiological activity disclosed in the prior art for the agents recited in the claims of my patent application, the specification provides the skilled worker in this field with enough information to alleviate a tumor in a human patient.

33. The agents described in items 34 to 37 are recited in only some of the claims in my patent application.

34. Type 1 Lymphocyte Attractant (e.g., see claim 37). My patent application discloses (e.g., at page 19, lines 12-22) that a type 1 lymphocyte attractant can be locally administered to the tumor site. It was known at the time I filed my patent application that leukocytes could be induced to migrate to a site of inflammation using various cytokines (see, e.g., Roussel et al., 1997, J. Leukocyte Biol. 62:356-362, of record). The skilled worker in this field would expect that local administration of one of these cytokines to a tumor would recruit additional leukocytes that exhibit a type 1 inflammatory response to the tumor (e.g., see Mantovani, 1999, Immunol. Today 20:254-257, of record). Attraction of additional type 1 lymphocytes to a tumor would be expected to enhance the anti-tumor type 1 inflammatory response to the tumor.

35. Autologous Leukocytes (e.g., see claim 40). My patent application discloses (e.g., at page 19, line 23, through page 21, line 2) that expanded, differentiated, or expanded and differentiated leukocytes can be provided to the tumor site. It was known at the time I filed my patent application that leukocytes could be obtained from a patient, cultured and expanded *ex vivo* and returned to the patient (e.g., see To et al., 2000, Laryngoscope 110:1648-1654, of record). The skilled worker in this field would expect that this would result in the presence of additional leukocytes to the site, whether they already exhibit the type 1

inflammatory response or are induced to exhibit this response by the type 1 inflammatory response-promoting agents at the site. The presence of additional leukocytes exhibiting a type 1 inflammatory response at the tumor site would be expected to enhance the anti-tumor effect attributable to the inflammatory response.

36. Memory Cell-Inducing Agent (e.g., see claim 41). My patent application discloses (e.g., at page 21, lines 13-20) that a memory cell-inducing agent can be administered to the patient. It was known at the time I filed my patent application that various agents such as IFN-alpha and IL-15 could be administered to a patient to enhance production of memory T-cells *in vivo* (see, e.g., Akbar et al., 2000, Immunol. Today 337-342, of record). The skilled worker in this field would expect that administration of one of these agents to a patient in whose tumor a type 1 inflammatory response had been induced would enhance production of immune memory cells. The skilled worker would expect that recurrence of the tumor would thereby be inhibited or prevented, because memory cells are known to enhance the immune system's ability to react more quickly and robustly to a recurrence of an antigen (such as a tumor of the same type).

37. Nutrition (e.g., see claim 42). My patent application discloses (e.g., at page 22, lines 7-22) that the patient's nutrition can be supplemented. It was known at the time I filed my patent application that various nutrients enhance functioning of the human immune system *in vivo* (see, e.g., Bendich, 1997, Nutrition 13:154-155; Weber et al., 1997, Nutrition, 13:450-460; Rayman, 2000, Lancet 356:233-241, all of record). The skilled worker in this field knows that appropriate nutrition is necessary for optimal immune system function, and that the anti-tumor type 1 inflammatory response induced by performing the methods claimed in my patent application can be enhanced by ensuring proper nutrition for the patient on whom the methods are performed.

38. As set forth in items 28 to 37, data has been reported in many journals that discloses the *in vivo* activities of the agents recited in the claims in my patent application. The skilled worker in this field would expect those reported results to be reproducible. The Examiner's objection that *in vivo* results cannot be predicted from *in vitro* data is inapplicable to my claimed methods for this reason. The methods claimed in my patent application represent a

synergistic combination of the disclosed activities of known agents in a way that was not previously contemplated by others. Now that the combination has been disclosed in my patent application, the skilled worker in this field who reads and follows my patent application is able to use the methods I have claimed therein to alleviate a tumor in a human patient.

Need for Relatively Little Experimentation

39. In the Office Action, the Examiner suggests that a skilled worker in this field would need to undertake undue experimentation in order to practice my claimed invention. I believe that this is untrue, for the reasons set forth in items 40-46.

40. The variable elements of my claimed inventions include i) the identity of the agents administered; ii) the dose of each agent to be administered; iii) the precise method by which the agents are administered; iv) the order in which the agents are administered; and v) the timing of the administrations. The variability of these elements and the descriptions offered in my patent application for each of these elements are discussed in items 41-45.

41. Identities of Agents. Where the identity of an agent is not specified in a claim, my patent application discloses multiple examples of such agents. In most, if not all instances, explicitly disclosed agents are also recited in dependent claims. A skilled worker in this field would not have difficulty referencing the literature to identify additional agents not disclosed in my patent application that exhibit the properties recited in the claims.

42. Doses of Agents. My patent application discloses appropriate doses of the agents recited in the claims. Furthermore, because each of the agents was previously known to exhibit the activity for which it is used, a skilled worker in this field can also consult the prior art to select appropriate doses of agents.

43. Route of Administration. The routes by which the agents recited in the claims are administered are not critical, except where "local" administration is recited. Even where "local" administration is recited, the precise method used to effect local administration is not critical. The route selected by a skilled worker in this field will depend on the location and nature of the tumor, the apparatus available to the worker, and the form in which the agent is

obtained. Selection of a route of administration given these variables is a normal function performed by workers in this field. My patent application provides the worker with all the guidance that is needed to select an appropriate route, in view of the worker's normal functions.

44. Order of Administration. The order in which the agents are administered is not critical, except where indicated in my patent application. Thus, my patent application provides all of the information that is needed to select an appropriate order of administration. Some preferred orders of administration are disclosed in my patent application (e.g., claim 66).

45. Timing of Administration. The timing of administration of the agents would be clear to a skilled worker in this field. The skilled worker would understand that the agents must be administered in a time frame in which the agents can have the cooperative effects indicated in my patent application. This knowledge exists in the art. Furthermore, my patent application discloses appropriate time frames for administration of the agents recited in the claims.

46. For the reasons set forth in items 41-45, a skilled worker in this field would be able to practice my invention without performing substantially any more experimentation than is normally done during customization of an anti-cancer therapy for individual patients.

Working Examples

47. The Examiner objects that my patent application does not include working examples wherein the claimed methods were actually practiced in humans. Human trials have not occurred because there are corporate funding and ethical clearance issues that have not yet been resolved. However, based on the *in vivo* data available in the art and the guidance provided in my patent application, a skilled worker in this field would expect the claimed methods to work as described in my patent application. The absence of clinical trials to date would not cause a skilled worker in this field to be unable to practice the methods that I have claimed in my patent application.

48. Even in the absence of working examples of the methods claimed in my patent application, a skilled worker in this field would consider the Xiang, To, Wong, Lowes, Khar, and the BCG references to indicate that induction of an anti-tumor type 1 inflammatory response in a human leads to tumor alleviation in the human (see items 20-25 of this Declaration). In view of the explanation provide herein (see items 28-38 of this Declaration) and in my patent application of how the steps recited in my claimed methods induce an anti-tumor inflammatory response in a human patient, the skilled worker in this field would expect that performance of my claimed methods on a tumor-afflicted human patient would lead to induction of death of at least some of the patient's tumor cells.

49. For the reasons set forth in items 47 and 48, a skilled worker in this field would believe that the Xiang, To, Wong, Lowes, Khar, and the BCG references indicate that the methods claimed in my patent application can be used to induce death of tumor cells in humans, even in the absence of working examples.

Summary

50. For all of the foregoing reasons, a skilled worker in the field of cancer therapy would, after reading my patent application, be able to practice the claimed methods of inducing death of tumor cells in a human patient. Although that worker might reasonably doubt that the claimed methods will work uniformly well for all patients or that tumors will be completely eliminated in all patients, the worker would expect at least some degree of tumor cell death will be induced in most patients. Because I have claimed only induction of tumor cell death in my patent application, the specification adequately discloses what I have claimed.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

1/03/2003
Date

Eugene Rousse
Dr. Eugene Rousse

Enclosures:
Greenberg, 1997, In: Medical Immunology, 9th ed., Stites et al., Eds., Appleton & Lange, Stamford, Connecticut, pp. 631-639
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